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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VENCI, DAVID J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,318	COSGROVE, DOMINIC E.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 25, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☒ Claim(s) *6,7,13,14,22 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 25, 2005, has been entered.

Currently, claims 1-23 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Declaration

The declaration under 37 CFR 1.132 filed April 25, 2005, is sufficient to overcome the rejection of claims 1-23 under 35 USC 112, first paragraph, for failing to comply with the written description requirement.

Claim Objections

Claims 6-7, 13-14 and 22-23 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Dependent claims 7, 14 and 23 do not further limit the subject matter of claims 1, 8 and 15, respectively, because claims 7, 14 and 23 do not

change the immunoreactivity of "at least one antibody" of claims 1, 8 and 15. Dependent claims 6, 13 and 22 broaden the subject matter of claims 1, 8 and 15, respectively, because the immunoreactivity of "at least one antibody" of claims 1, 8 and 15 is broadened to include SEQ ID NO:1 from a mouse.

Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form.

Claim Rejections - 35 USC § 112

Claims 1-7 and 15-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' specification provides a qualitative determination usherin protein in various tissues. For example, applicants' specification teaches that usherin protein is immunohistochemically detected in testis, epididymus, ovary, spleen, submaxillary gland, intestine, retina and cochlea tissues (see specification, p. 38, lines 3-6 and 11-13). In addition, Applicants' specification teaches that usherin protein is not immunohistochemically detected in brain, skin, lung, muscle, liver and kidney tissues (see specification, p. 38, lines 6-8).

Applicants' immunohistochemical data do not set forth any quantitative correlation between the level of usherin protein expression and Usher syndrome Type IIa. Applicants' specification does not appear to set forth any clinical data in support of a correlation between usherin protein expression levels and Usher syndrome Type IIa.

According to the decision in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the state of the prior art appears to be relatively uninformed, given that the usherin gene/protein was discovered and published a mere 2 years prior to Applicant's effective filing date. Aside from Applicant's post-filing date immunohistochemical localization data presented by Bhattacharya et al., 163 HEARING RESEARCH 1 (2002), and rtPCR expression analysis presented by Cohn et al., 114 LARYNGOSCOPE 1310 (2004), the prior art appears silent with respect to the usherin protein per se. Thus, absent necessary objective evidence, a person of ordinary skill could not reasonably conclude a relationship between usherin protein expression levels and disease state.

With respect to the level of predictability in the art, the state of the prior art generally recognizes that the relationship between protein expression levels (e.g. usherin protein) and disease state (e.g. Usher syndrome Type IIa) is unpredictable. According to Strongin (1993, "Sensitivity, Specificity and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications", in Laboratory Diagnosis of Viral

Infections, Lennette, e., ed., Marcel Dekker, Inc., New York, pp. 211-219) a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the following: (1) the sensitivity of the assay; (2) the true-positive test rate; (3) the false-negative test rate; (4) the specificity, or percentage of patients without the disease who will display a negative result; (5) the true-negative test rate; (6) the false-positive test rate; (7) the predictive value, or the probability that the test result is correctly indicating the presence or absence of the disease; (8) the prevalence, or number of patients in any given population that have the disease in question; (9) the efficiency or percentage of all results that are true; (10) the accuracy of the recited diagnostic assay.

Additional considerations must also be examined to enable the clinician to practice the invention, including assessment of the following: (1) when is the maximum sensitivity desired? (2) when is the maximum specificity desired?; (3) when is the maximum efficiency desired?; (4) How is the maximum sensitivity or specificity achieved?; (5) how is the predictive value maximized? An essential understanding of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test.

Here, Applicants' specification does not appear to provide direction or working examples for any of the aforementioned considerations.

Since the specification lacks any teaching of a method for correlating usherin protein expression levels and Usher syndrome Type IIa, or whether any considerations were given to any of the characteristics stated above, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the recitation of "wherein the biological sample is from... an individual not having Usher syndrome" is indefinite because it seemingly contradicts the purpose of the method as set forth in the preamble.

In claim 1, the recitation of "the usherin protein" lacks antecedent basis.

In claims 4, 11, 18 and 21, the recitation of "and combinations thereof" is indefinite because it is not clear whether/how detectable labels are both radioactive and non-radioactive.

In claims 5 and 12, the recitation of "or combinations thereof" is indefinite because it is not clear whether/how antibodies are both monoclonal and polyclonal.

In claims 6, 13 and 22, the recitation of "and combinations thereof" is indefinite because it is not clear whether more than one antibody species is required, or whether bispecific antibodies are required.

Claim Rejections - 35 USC § 103

Claims 8-9 and 12-14 rejected under 35 U.S.C. 103(a) as being unpatentable over Eudy et al., 280 SCIENCE 1753 (1998), in view of Pestronk (US 5,985,578).

Eudy et al. describe a method for detecting human usherin protein having SEQ ID NO:4 (see Fig. 4(A)) in order to correlate with Usher syndrome Type IIa (see p. 1756, col. 1, last paragraph, "development of a differential diagnostic tool for patients with Usher syndrome").

Eudy et al. do not describe an immunoassay.

However, Pestronk describes an immunoassay method of detecting disease-associated antigens comprising the steps of: obtaining a tissue sample (see col. 19, lines 26-27, "a sample which is a section of peripheral nerve or other tissue"), wherein the tissue normally includes an antigen in an individual not having the syndrome (see col. 19, lines 21-22, "depleted of a particular antigen"), incubating the antigen with an immunoreactive antibody to produce an immunoconjugate (see col. 19, lines 17-18), evaluating the presence of the immunoconjugate (see col. 19, lines 19-20, "aberrancies in the distribution or level of expression"), and correlating the presence or absence of the immunoconjugate with the syndrome (see col. 19, lines 23-25).

Therefore, it would have been obvious for a person of ordinary skill in the art to detect human usherin protein having SEQ ID NO:4, as described by Eudy et al., with the immunoassay of Pestronk because Pestronk discovered that immunoassays can be used to detect glycosylated protein immunoconjugates to diagnose neurological disease states (see col. 9, lines 21-23), which allows for the categorization of patients into groups that share similar prognoses and treatment options (see col. 9, lines 49-50).

With respect to claim 9, Eudy et al. describe an eye sample (see p. 1756, endnote 15).

With respect to claim 12, Pestronk describes monoclonal antibodies (see col. 18, lines 18-21).

With respect to claims 13-14, Eudy et al. describe polypeptides having SEQ ID NO: 2 and SEQ ID NO:4 (see Fig. 4(A)).

Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eudy et al., 280 SCIENCE 1753 (1998) and Pestronk (US 5,985,578) as applied to claim 8, and further in view of Maggio, ENZYME-IMMUNOASSAY, CRC Press (1980).

Eudy et al. and Pestronk describe a method for detecting human usherin protein as substantially described supra. Eudy et al. and Pestronk do not teach a detectably labeled antibody (claims 3 and 10).

However, Maggio teaches the use of labeled antibodies (see p. 61, Table 3) for detecting analytes. Therefore, it would have been obvious for a person of ordinary skill in the art to practice the method for detecting human usherin protein, as taught by Pestronk and Eudy et al., with a labeled antibody because Maggio teaches that a labeled antibody "allows for minimal number of steps in protocol" (see p. 61, Table 3, "Advantages").

With respect to claim 11, Maggio teaches non-radioactive labels (see Title).

Response to Arguments

In prior Office Action, claims 1, 8 and 15 were rejected under 35 USC 112, first paragraph, for failing to comply with the enablement requirement. In response, Applicant argues that paragraphs 4-8 and Figs. A and B of Applicant's declaration filed pursuant to 37 CFR 1.132 on April 25, 2005, is sufficient to overcome this rejection. Specifically, Applicant's declaration appears to summarize the methodology and data presented by Cohn et al., 114 LARYNGOSCOPE 1310 (2004). The salient information presented in Applicant's declaration and presented by Cohn et al. are:

1. Anti-usherin antibodies were developed against peptides having SEQ ID NO:2 of the usherin protein (see Applicant's declaration, paragraph 5).

2. Said anti-usherin antibodies were used to determine the presence of usherin protein in patients having a "2299delG mutation" (see Cohn et al., p. 1311, col. 1, Subject Selection). The "2299delG mutation" appears to be a truncated form of said usherin protein.

3. Said anti-usherin antibodies did not bind to said truncated form of said usherin protein from patients having said "2299delG mutation" (see Applicant's declaration, paragraph 7; see Cohn et al., Fig. 2).

4. Besides said "2299delG mutation," other usherin protein mutations exist that result in Usher syndrome type IIa (see Cohn et al., Table I).

5. Said other usherin protein mutations may bind to said anti-usherin antibodies, which may produce false negative results (see Cohn et al., p. 1312, col. 2, "If we assume that all missense mutations produce an antigenically active protein... we would expect to observe a negative result for usherin immunostaining... in at least 61% of patients with Usher syndrome type IIa" (internal parentheticals omitted)).

6. The diagnostic ability of said anti-usherin antibodies developed against peptides having SEQ ID NO:2 of the usherin protein is limited to patients with Usher syndrome type IIa who are homozygous for said "2299delG mutation" (see Cohn et al., p. 1312, col. 1-2, "We have provided proof of a concept that supports the use of usherin antibody for immunostaining of human minor salivary gland tissue... in patients with Usher syndrome type IIa who are homozygous for 2299delG" (emphasis added)).

From the above information, it is clear that the diagnostic ability of said anti-usherin antibodies developed against peptides having SEQ ID NO:2 of the usherin protein is currently limited to patients with Usher syndrome type IIa who are homozygous for said 2299delG mutation. For patients having other mutations resulting in Usher syndrome type IIa, the diagnostic ability of said anti-usherin antibodies developed against peptides having SEQ ID NO:2 of the usherin protein is, at best, unknown.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be

reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J Venci
Examiner
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7/11/05